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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/479,997	06/07/95	ENGELHARDT	ENZ-5(D6)(C2)

RONALD C. FEDUS, ESQ.
ENZO BIOCHEM, INC.
527 MADISON AVENUE, 9TH FLOOR
NEW YORK NY 10022

18M2/0106

EXAMINER
HOOTTEMAN, S

ART UNIT	PAPER NUMBER
1807	16

DATE MAILED: 01/06/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/479,997

Applicant(s)

Engelhardt et al.

Examiner

Scott W. Houtteman

Group Art Unit

1807



☒ Responsive to communication(s) filed on Nov 24, 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 278-453

is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 278-453 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to: **Art Unit: 1807**; Examiner: Scott Houtteman.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 278-453 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly submitted claims 278-453 are drawn to nucleotides, polynucleotides, etc. and compositions containing these products. Descriptive support was not pointed out, nor was it found for numerous limitations.

Sig moiety is newly limited to "at least three carbon atoms having the "Sig" moiety. The points of attachment are limited in claims that newly recite chemical structures (for example claims 373, 405 and 433). Specific "Sigs" which attached to are attached to the phosphate are newly identified, for example, a glycosidic linkage moiety, biotin, iminobiotin, ferritin, an antigen, a hapten, an antibody, specific. Finally, the phosphate moiety has been newly limited to "a di-phosphate or a tri-phosphate moiety."

sites of attachment, specific types of chemical linkages and that "sig" be "at least three carbon atoms," etc.

The only support in the original disclosure was in a passage on pages 96-97 which begins "By way of summary" and nine other clauses pointed out in Applicant's response filed 11/24/97, pages 39-40.

These passages define the attachment of "Sig" to the phosphate in generic terms. Sig is "covalently attached" to either base, sugar or phosphate. However, there is no *explicit* description of the various claimed products bound to the phosphate anywhere in the specification.

In contrast, the base-linked "Sig" moieties have numerous complex chemical reactions which are necessary to synthesis the various products. These reactions include various solvents, reactants and protecting groups which are necessary so that only the base was modified and not the reactive groups on the sugar or phosphates. Thus, an explicit description of the "phosphate-Sig" reactions would have been expected in order for a skilled artisan to have reasonably concluded that the original disclosure evidenced "possession" of the currently claimed invention.

Thus, in view of the generic disclosure and the absence of any specific "phosphate-Sig" reactions; and in view of the complex nature of reactions of labels to DNA, the skilled artisan would not have reasonably expected this specification to put the artisan in possession of the invention as now claimed.

Since support for these claims was not found where pointed out nor elsewhere in the specification, these claims are considered "new matter."

3. Applicant argues, briefly, support is in various paragraph and clauses within the spec.

This argument is not persuasive. These portions of the specification are merely generic recitations not support for the specific claim limitations.

4. Applicant argues that, according to the Engelhardt declaration filed 11/24/97, Example V and Halloran reference provide support. This argument is not persuasive. These methods do not mention DNA labeled at the phosphate moiety and thus do not provide a written description of the claimed invention.

5. Applicant further argues, briefly, that 16 references describing reactions to phosphorous, oxygen and coupling nucleic acids to other polymers provide support. This argument is not persuasive. These references do not describe the specific products in the claims but merely describe reactions that can be used to synthesize the claimed products if used on DNA. However, the reactions are are used on other reactants in the references.

6. Applicant argues, briefly, that modifications of phosphate, sugar and base moieties are "functional equivalents;" that the reactions described for the base moiety are applicable to the sugar and phosphate moiety as well and that these reactions "were known in the art for modifying the phosphate moiety of a nucleotide.

These arguments are not persuasive. The standard for written description is not merely that one can find the limitations in the prior art or that the limitations are well known. The

standard is that the specification must reasonably convey that the inventor had possession of the specific claimed invention. The limitations of the prior art can only be evidence of "possession" if they must necessarily be a part of the current specification. No portion of the specification was pointed out which is necessarily linked to any of the given prior art teachings.

7. Claims 278-453 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not disclosed in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 278-453 are broadly drawn to nucleotides having various "Sig moieties" attached to the phosphate moiety.

The specification contains a sufficiently detailed disclosure, such as in Examples I-VII, to enable the construction of "sig-base" nucleotides, that is nucleotides in which the "Sig" moiety is linked to the base. It is noted that these reactions contain many specific solvents, reactants and protecting groups. This detailed disclosure enables one to obtain a reasonable product yield, a product of suitable stability for its intended use in nucleic acid detection assays and a product reasonably free of unwanted side products in which the Sig moiety is attached at the wrong places on the nucleotide.

However, there is no analogous disclosure for the attachment of the "Sig-phosphate" nucleotides. The broadly claimed "Sig moieties" include a very diverse population of molecules, from simple inorganic compounds like radioactive Cobalt to the complex organic molecules like enzymes. Accordingly, there are a vast number of possible chemical reaction schemes one could

attempt. Without specific guidance or examples, the skilled artisan would expect that the vast majority of these reaction schemes would fail. Either the product yields would be low, the products would be too unstable or the products would be too hard to purify away from extraneous side products.

It is difficult to predict the behavior of a complex organic molecule with numerous functional groups: primary amines, carboxyl groups and alcohol groups. There is no way to establish, before the fact, which reaction conditions will result in high yields and stable products that can be purified from extraneous byproducts.

The level of skill is high in this field. Nevertheless, in view of the large scope of these claims, the lack of any guidance or specific examples, the high degree of unpredictability, the complex nature of the invention which requires both inorganic and organic chemical syntheses; it would have required undue experimentation to enable a reasonable number of embodiments within the scope of these claims.

8. Applicant argues, briefly, that only minimal experimentation was required to practice the claimed invention in view of 16 references which teach the relevant reactions. This argument is not persuasive. It is undue experimentation to expect the skilled artisan (1) to search out and find the references and (2) know which references to use. It is important to note that none of the references are specifically drawn to synthesis of the claimed products.

9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 278-453 are rejected under 35 U.S.C. § 103 for being unpatentable over Gohlke in view of Sodja et al., Nucleic Acids Res, 5(2):385-401, 1978 (Sodja) and further in view of applicants admissions.

Gohlke discloses, for example, col 3, lines 3-22, the use of detection assays using labels such as fluorescent compounds, chemiluminescent compounds and enzymes like β -galactosidase and, in col. 2, lines 32 and 35, antibodies.

Sodja teaches on page 386 the attachment, to the free 3' OH end of RNA, an avidin-ferritin label using the lysine groups of the polypeptide cytochrome-c).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the labels of Sodja in the methods of Gohlke for the expected benefit of using electron microscopic detection of the bound label.

Applicant admits, in the amendment filed 11/24/97, on page 43, that "Numerous reactions were known in the art for modifying the phosphate moiety of a nucleotide" and "explicit description of such known reactions would not have been necessary." It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the "numerous reactions known in the art" for the expected advantage of labeling DNA.

11. Applicant argues that immunoassays are non-analogous to nucleic acid labeling assays. This argument is not persuasive. Many of the same labels were used in both assays, for example biotin. Also, Gohlke et al., a immunoassay publication is using a nucleotide.
12. Applicant argues that immunoassay modifications would not have been expected to function in nucleic acid technology because of the different "geometry" of the interactions between immunological products and the "two-dimensional" hybridization of nucleic acids. This argument is not persuasive. There is no evidence presented of the state of mind of scientists in immunology and nucleic acid hybridization. The merely conclusory statements of counsel on this important and speculative matter carry little weight.

13. Applicant argues that because of the reaction scheme, Sodja breaks open the sugar ring of the nucleotide and are "not remotely connected to the invention at hand." First, the claims are not limited to either an open sugar ring or a closed sugar ring. The claims merely recite "a sugar moiety."

Second, since the modified nucleic acid can still be used in a hybridization assay it is unclear why the state of the sugar moiety on the terminal base of a nucleotide would be at all critical to the invention. Thus, either an open or closed sugar ring are art recognized alternatives. The ordinary artisan would have expected either to work in a nucleic acid hybridization assay.

Third, applicant admits that "Numerous reactions were known in the art for modifying the phosphate moiety of a nucleotide." (See the 16 references on pages 45 and 46 of the Amendment filed 11/24/97. Thus, to the extent that an open ring would be a disadvantage, the ordinary artisan would be motivated to use any of these "numerous reactions."

14. Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Art Unit 1807. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Art Unit 1807 Fax number is (703) 305-7401.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott Houtteman whose telephone number is (703) 308-3885. The examiner can normally be reached on Tuesday-Friday from 8:30 AM - 6:00 PM. The examiner can also be reached on alternate Mondays.

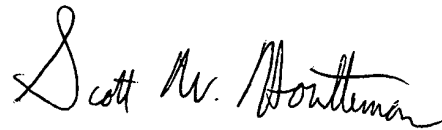
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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott Houtteman
January 5, 1998



**SCOTT W. HOUTTEMAN
PRIMARY EXAMINER
GROUP 1800**